REMARKS

Applicants amended the specification to obviate the objection to the trademarked terms in paragraphs 231 and 234 of the specification. In addition, Applicants have presented additional claims 61-66 corresponding to the elected sequence., SEQ ID NO:11. An indication of allowance of all claims is respectfully requested.

This Reply is Responsive to the Office Action mailed on November 13, 2007. At the outset Applicants note with appreciation that the elected claims are indicated to be free of any prior art rejection. However, these claims stand rejected under 35 USC 112 first paragraph. This rejection and objections to the specification are addressed infra.

Turning now to the Office Action, the maintenance of the Restriction Requirement and the election of species requirement are noted. The Examiner indicates that she is not bound by the PCT Treaty and the prior determination of other PCT and national Patent Office determinations. The position of the Examiner is respectfully traversed. While the Examiner is correct in that she is not bound to follow the decisions made by other examining officials, since this is a National stage application of a PCT application that designated the United States, she is required to follow the PCT rules with respect to Restriction practice and unity of invention. Applicants respectfully submit that if these rules are followed that claims 43-60 and new Claims 61-66 should be examined together, especially given the fact that the elected species has been found to be free of the prior art.

With respect thereto, Applicants maintain respectfully that the Restriction Requirement violates the PCT rules and US restriction practice governing patent applications filed under 35 USC 371 since it is in conflict with Article 127(1) of the PCT wherein it is stated that no national law shall require compliance with requirements correlating to the form or context of the international application different from or additional to those in which are provided in the Treaty and the Regulations. Article 27(1) is further clarified in the PCT guidelines under Item 138, wherein it is stated that an international application which complies with the unity of invention requirement laid down in Rule 13 PCT must be accepted in all the designated and elected offices. Applicants' previous traversal and remarks are incorporated by reference herein.

In addition. Applicants acknowledge their previous election for purposes of examination of the nucleic acid sequence contained in SEQ ID NO:11 which correspond to a detected

transcriptional product which is encompassed by the elected assay methods. This sequence is recited in Claim 50 which depends from claim 49 which in turn depend from claims 43, 44, 45, 46 or 47. Applicants respectfully request that since the elected species is free of the prior art that the Examiner extends the search to the other sequences recited in the claims.

With respect thereto, Applicants again note that the sequences in SEQ IDs no. 12 to 18 correspond to single AMB1/CLLU1 exon sequences, which never exist as "single transcripts", rather all AMB1/CLLU1 transcripts, except 1, are composed of several exons. All exons are present within the genomic sequence included in SEQ ID no. 5. It has been discovered that there is a primary AMB1/CLLU1 transcript that at least covers from pos. 8,950 to pos. 71,099 in the sequence included in SEQ ID No. 5. Therefore, any transcript that includes the sequence from the start of the AMB1/CLLU1 primary transcript (pos. 8,950 in SEQ ID no. 5) as the first exon, can be used for B-CLL diagnostics. At least in view thereof, Applicants believe that the recited group of sequences in the elected claims corresponds to a single unitary invention.

With particular respect to the elected sequence, this cDNA sequence corresponds to a transcript the inventors have detected to be present in CLL cells, and which includes most of the sequences relevant for B-CLL diagnostics, i.e., SEQ ID No. 11.. By use of SEQ ID No:11 only one single exon is potentially not detected from an "odd" down-stream cDNA. Expression of that cDNA also give "the prognosis", but ONLY if exon 1 is used as the first exon. Exon 1 is part of both SEQ IDs 1, 5 and 11.

As noted, there is a single exon which potentially is not detected using assays limited to detecting SEQ ID No. 11. This exon also forms part of another mRNA, which starts another place. For the foregoing reasons, Applicants respectfully submit that the Examiner at least extend her search to assays which detect for any one of the transcription products contained in SEQ ID NO: 1, 5 or 11 as this provides for a more comprehensive and biologically relevant assay. Therefore, Applicants request that Claims 48, 51, 52, and 55-60 and the remaining claims be examined in their entirety.

Objections to the Specification Concerning Formalities

The objection to the specification concerning reference citations is noted. Applicants respectfully submit that the material references in accord with the duty of disclosure rules have been made of record in proper Information Disclosure Statements.

The objection to the typos in the specification in paragraph [232] is noted. A paragraph correcting the typo is contained in this amendment.

The objection to certain sequences in the disclosure is noted. Applicants respectfully note that a Sequence Listing was previously submitted and found to be acceptable. An examination of the elected subject matter was made based on this Sequence Listing. The sequences at pages 32 and 39 noted refer to commercially available primers and synthetic peptides which are not necessary for an understanding or examination of any of the claims pending herein. Withdrawal of this objection is respectfully requested.

The objection to certain trademark symbols is also noted. An amendment to the specification herein is included in this Response which adds the omitted trademark information in substitute paragraphs [231] and [234]. Based thereon, withdrawal of this objection is respectfully requested.

Claim Rejections - 35 USC § 112

Claims 43-47, 49, 50, 53 and 54 stand rejected under 35 USC§112 . The basis of the rejection is the Examiner's preliminary finding that the specification only enables a method of diagnosing a poor prognosis of B-CLL by detecting the presence of the exon 2/exon 3 splice junction in an AMB-1 transcript, but allegedly does not enable a method for detecting a subtype of B-CLL with poor prognosis by detecting any expression product within SEQ ID NO:12-18. The position of the Examiner is respectfully traversed.

Applicants respectfully submit that the as-filed application clearly enables the scope of claims pending herein and submit that practice of the invention would not require undue experimentation. Also, Applicants respectfully submit that given the clear novelty of the claimed detection methods and the importance of an improved method for detecting this disease and its prognosis, which afflicts and indeed kills many individuals annually, that this application should be allowed as it will provide an improvement in identifying individuals with this disease and their prognosis relative to other individuals and furthermore will facilitate designing and implementing appropriate therapeutic regimens based on this diagnosis. Based thereon, Applicants strongly traverse the rejection and strongly believe that the specification clearly establishes to a person skilled in the art based on the data contained herein that the presence of "any AMB-1 transcript" correlates with the un-mutated IgV_H genes subtype of B-CLL.

In particular, the data shown in figure 3 of the present application clearly establishes that Applicants are in possession of and sufficiently describe a method of reproducibly detecting AMB-1 transcripts in cell extracts by means of Northern blotting, described in [0247]. It should be noted

that in this Figure the left hand lanes UPN1, UPN4, and UPN7 are samples from B-CLL patients with un-mutated IgV_H genes, whereas the lanes UPN19, UNP9, UPN10, UPN13, and UPN21 are samples from B-CLL patients with mutated IgV_H genes. On the right are samples from tissues of healthy persons. The blot is probed with a fragment of Exon 3 (SEQ ID No: 16). The data clearly confirms the presence of at least three transcripts in samples of subtype of B-cells with un-mutated IgV_H genes – one transcript with a size less than the 1.8 kb (18S RNA marker), another larger transcript between the 1.8 kb 18S RNA marker and another transcript below the 5.0 kb 28S RNA marker. The third long transcript in the top of the blot corresponds to the primary un-spliced.

This Northern blot confirms that transcripts comprising Exon 3 correlate to and may be detected in B-CLL patients with un-mutated IgVH genes. On the other hand, transcripts comprising Exon 3 is not detected in samples from B-CLL patients with mutated IgV_H genes and samples from tissues of healthy persons. Thus, the presence of AMB-1 transcripts comprising Exon 3 (SEQ ID No: 16) correlates to the presence of B-cells with un-mutated IgV_H genes.

Moreover, as described in the as-filed application, the detection of the primary transcript is also restricted to the subtype of B-cells with un-mutated IgV_H genes, thus confirming that spliced AMB-1 transcripts originating from the common un-spliced primary is not detected in mutated IgV_H genes and samples from tissues of healthy persons. By contrast, the absence of any AMB-1 transcript is reflected by the absence of the common AMB-1 primary transcripts.

The absence of any AMB-1 transcript reflected by the absence of the common AMB-1 primary transcripts in tissues of healthy persons is further confirmed in Figure 8, [0245] and [0247] of the present application. Figure 8 shows the overview of the filter used for RNA dot blot probing of a fragment of Exon 3, which comprises 68 different human tissues and 12 human cell lines. The RNA dot blot failed to detect CLLU1 transcript even at very long exposures. Signal was only observed on chromosomal DNA and *E.coli* chromosomal DNA due to contamination of the probe with small traces of E. coli chromosomal DNA.

Therefore, Applicant submits that specification as filed provides that the presence of any AMB-1 transcript, and in particular the nucleic acid sequences recited in the pending claims correlates with B-CLL patients with un-mutated IgV_H genes. The specification also discloses that the un-mutated IgV_H subtype of B-CLL is associated with poor prognosis. Thus, the specification undeniably clearly discloses that the presence of any AMB-1 transcript is associated with poor prognosis and further provides nucleic acid and polypeptide assay detection methods as claimed which could readily be practiced by a person having ordinary skill in the art in order to determine

whether an individual .should be diagnosed as having a subtype of B-cell chronic lymphocytic leukemia (B-CLL) associated with a poor prognosis.

In addition, Applicants respectfully submit that no evidence or convincing scientific reasoning has been set forth which refutes the underlying data in this application which convincingly establishes that the specification is enabling for the entire scope of the claims pending herein. Based thereon, withdrawal of the 112 first paragraph rejection in its entirety is respectfully requested.

No fees are believed to be due for this amendment. However, the Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 C.F.R. § 1.16 and § 1.17 associated with this communication or credit any overpayment to the deposit account of Hunton & Williams, **Deposit Account Number 50-0206**.

Respectfully submitted,

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Dated: 4/14/08 By: _____

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